

In the Claims

Please replace all prior versions, and listings, of claims in the application with the following list of claims:

1. (Currently amended) An isolated anti-Tumor Necrosis Factor-alpha (anti-TNF-alpha) polypeptide comprising at least one anti-TNF-alpha single domain antibody which is a Camelidae variable domain derived from a heavy chain antibody devoid of a light chain (VHH) or a humanized Camelidae VHH, wherein the polypeptide does not include a light chain.
2. (Currently amended) An anti-TNF-alpha polypeptide according to claim 1 wherein ~~[[a]]~~ at least one single domain antibody corresponds to a sequence represented by comprises the amino acid sequence of any of SEQ ID NOs: 1 to 16 and 79 to 84.
3. (Previously presented) An anti-TNF-alpha polypeptide according to claim 1 further comprising at least one single domain antibody directed against a serum protein.
4. (Previously presented) An anti-TNF-alpha polypeptide according to claim 3 wherein said serum protein is any of serum albumin, serum immunoglobulins, thyroxine-binding protein, transferrin, or fibrinogen.
5. (Currently amended) An anti-TNF-alpha polypeptide according to claim 3 wherein the anti-serum protein single domain antibody ~~correspond to a sequence represented by~~ comprises the amino acid sequence of any of SEQ ID NOs: 26 to 29 and 85 to 97.
6. (Currently amended) An anti-TNF-alpha polypeptide according to claim 3 ~~corresponding to a sequence represented by~~ comprising the amino acid sequence of any of SEQ ID NOs: 30 to 43.
7. (Currently amended) An anti-TNF-alpha polypeptide according to claim 1 further comprising at least one single domain antibody selected from the group consisting of anti-

interferon-gamma (anti-IFN-gamma) single domain antibody, anti-TNF-alpha receptor single domain antibody and anti-IFN-gamma receptor single domain antibody.

8. (Previously presented) An anti-TNF-alpha polypeptide according to claim 1, wherein the number of single domain antibodies directed against TNF-alpha is at least two.

9. (Withdrawn and currently amended) An anti-TNF-alpha polypeptide according to claim 8 ~~corresponding to a sequence represented by~~ comprising the amino acid sequence of any of SEQ ID NOs: 73 to 76.

10. (Currently amended) An anti-TNF-alpha polypeptide according claim 1 wherein at least one single domain antibody is a humanized *Camelidae* [[VHHs]] VHH.

11. (Withdrawn and currently amended) An anti-TNF-alpha polypeptide according to claim 10 wherein the [[a]] humanized *Camelidae* VHH ~~corresponds to a sequence represented by~~ comprises the amino acid sequence of any of SEQ ID NOs: 17 to 19 and 21 to 24.

12. (Currently amended) A composition comprising an anti-TNF-alpha polypeptide according to claim 1 and at least one single domain antibody from the group consisting of anti-interferon-gamma (anti-IFN-gamma) single domain antibody, anti-TNF-alpha receptor single domain antibody and anti-IFN-gamma receptor single domain antibody, ~~for simultaneous, separate or sequential administration to a subject.~~

13. (Withdrawn and currently amended) An anti-TNF-alpha polypeptide according to claim 7 wherein the at least one anti-IFN-gamma single domain antibody ~~corresponds to a sequence represented by~~ comprises the amino acid sequence of any of SEQ ID NOs: 44 to 72.

14. (Canceled)

15. (Canceled)

16. (Previously presented) An anti-TNF-alpha polypeptide according to claim 1 wherein the at least one single domain antibody is a *Camelidae* VHH.
17. (Withdrawn) A nucleic acid encoding an anti-TNF-alpha polypeptide according to claim 1.
18. (Withdrawn) A method of identifying an agent that modulates the binding of an anti-TNF-alpha polypeptide to Tumor Necrosis Factor-alpha comprising the steps of:
- (a) contacting an anti-TNF-alpha polypeptide of claim 1 with a target that is Tumor Necrosis Factor alpha, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and
 - (b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the binding in the absence of said candidate modulator, identifies said candidate modulator as an agent that modulates the binding of an anti-TNF-alpha polypeptide and Tumor Necrosis Factor-alpha.
19. (Withdrawn) A method of identifying an agent that modulates Tumor Necrosis Factor-alpha-mediated disorders through the binding of an anti-TNF-alpha polypeptide to Tumor Necrosis Factor-alpha comprising:
- (a) contacting an anti-TNF-alpha polypeptide of claim 1 with a target that is Tumor Necrosis Factor alpha, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and
 - (b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the binding in the absence of said candidate modulator, identifies said candidate modulator as an agent that modulates Tumor Necrosis Factor-alpha mediated disorders.
20. (Withdrawn) A method of identifying an agent that modulates the binding of Tumor Necrosis Factor alpha to its receptor through the binding of an anti-TNF-alpha polypeptide to Tumor Necrosis Factor-alpha comprising:

- (a) contacting an anti-TNF-alpha polypeptide of claim 1 with a target that is Tumor Necrosis Factor-alpha, in the presence and absence of a candidate modulator under conditions permitting binding between said polypeptide and target, and
- (b) measuring the binding between the polypeptide and target of step (a), wherein a decrease in binding in the presence of said candidate modulator, relative to the binding in the absence of said candidate modulator, identifies said candidate modulator as an agent that modulates the binding of Tumor Necrosis Factor-alpha to its receptor.
21. (Previously presented) A kit for screening for agents that modulate Tumor Necrosis Factor-alpha-mediated disorders comprising an anti-TNF-alpha polypeptide of claim 1 and Tumor Necrosis Factor-alpha.
- 22.-25. (Canceled)
26. (Withdrawn) A method for treating and/or preventing and/or alleviating disorders relating to inflammatory reactions comprising administering to a subject in need of such treatment an effective amount of the an anti-TNF-alpha polypeptide of claim 1.
27. (Canceled)
28. (Withdrawn) A method for treating and/or preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance. comprising administering to a subject in need of such treatment an anti-TNF-alpha polypeptide of claim 1 that passes through the gastric environment without the substance being inactivated.
29. (Canceled)
30. (Withdrawn) A method for treating and/or preventing and/or alleviating disorders susceptible to modulation by a TNF-alpha modulating substance delivered to the vaginal and/or rectal tract, or the nose, upper respiratory tract and/or lung, comprising administering to the

vaginal and/or rectal tract, or the nose, upper respiratory tract and/or lung, of a subject in need of such treatment an effective amount of an anti-TNF-alpha polypeptide of claim 1.

31.-33. (Canceled)

34. (Withdrawn) A method for treating and/or preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance delivered to the intestinal mucosa, wherein said disorder increases the permeability of the intestinal mucosa, comprising administering to the intestinal mucosa of a subject in need of such treatment an anti-TNF-alpha polypeptide of claim 1.

35. (Canceled)

36. (Withdrawn) A method for treating and/or preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance, comprising administering to a subject in need of such treatment an anti-TNF-alpha polypeptide of claim 1 that passes through the tissues beneath the tongue effectively.

37. (Canceled)

38. (Withdrawn) A method for treating and/or preventing and/or alleviating the symptoms of disorders susceptible to modulation by a TNF-alpha modulating substance, comprising administering to a subject in need of such treatment an anti-TNF-alpha polypeptide of claim 1 that passes through the skin effectively.

39. (Withdrawn) A method according to any of claims 26, 28, 30, 34, 36, and 38, wherein said disorders are any of inflammation, rheumatoid arthritis, Crohn's disease, ulcerative colitis, inflammatory bowel syndrome, multiple sclerosis, Addison's disease, Autoimmune hepatitis, Autoimmune parotitis, Diabetes Type I, Epididymitis, Glomerulonephritis, Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, Hemolytic anemia, Systemic lupus erythematosus, Male infertility, Multiple sclerosis, Myasthenia Gravis, Pemphigus, Psoriasis,

Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Scleroderma, Sjogren's syndrome, Spondyloarthropathies, Thyroiditis, and Vasculitis.

40. (Previously presented) A composition comprising the anti-TNF-alpha polypeptide of claim 1 and a suitable pharmaceutical vehicle.

41. (Withdrawn) A method of diagnosing a disorder characterised by the dysfunction of Tumor Necrosis Factor-alpha comprising:

- (a) contacting a sample with an anti-TNF-alpha polypeptide of claim 1,
- (b) detecting binding of said polypeptide to said sample, and
- (c) comparing the binding detected in step (b) with a standard, wherein a difference in binding relative to said sample is diagnostic of a disorder characterised by dysfunction of Tumor Necrosis Factor-alpha.

42.-43. (Canceled)

44. (Withdrawn) A method for purification of Tumor Necrosis Factor-alpha, comprising contacting a sample with the anti-TNF-alpha polypeptide of claim 1.

45. (Withdrawn) A method for inhibiting the interaction between Tumor Necrosis Factor-alpha and one or more Tumor Necrosis Factor-alpha receptors, comprising contacting Tumor Necrosis Factor-alpha with the anti-TNF-alpha polypeptide of claim 1.

46. (Withdrawn) A method for producing an anti-TNF-alpha polypeptide of claim 1 comprising the steps of:

- (a) obtaining double stranded DNA encoding a *Camelidae* VHH directed to Tumor Necrosis Factor alpha,
- (b) cloning and expressing the DNA selected in step (b).

47. (Withdrawn) A method of producing an anti-TNF-alpha polypeptide of claim 1 comprising:

- (a) culturing host cells comprising nucleic acid that encode an anti-TNF-alpha polypeptide of claim 1, under conditions allowing the expression of the polypeptide, and,
 - (b) recovering the produced polypeptide from the culture.
48. (Withdrawn) A method according to claim 47, wherein said host cells are bacterial or yeast.
49. (Canceled)